

wherein each of Y, X and R individually is selected from the group consisting of hydrogen, hydroxy, halo, CF₃, NO₂, CN, NH₂, COR¹ and CO₂R² wherein R¹ is selected from the group consisting of alkyl, aryl, alkaryl, and NH₂, and R² is selected from the group consisting of alkyl, aryl, and aralkyl, and provided that at least one of Y, X and R in formula I is other than hydrogen; or pharmaceutically acceptable salt thereof.

In the Abstract:

Please insert the Abstract attached hereto as a separate page.

REMARKS/ARGUMENTS

Claims 1-16 are now in the application. Claims 1 and 7-11 are drawn to the elected invention. Claims 2-6 and 12-16 are drawn to non-elected inventions and may be canceled by the Examiner upon the allowance of the claims directed to the elected invention.

Claims 1, 2, 4 and 16 have been amended to recite "or pharmaceutically acceptable salt thereof" as suggested by the Examiner. The amendment to the claims is for the purpose of clarification and not to limit the scope of the claims.

The rejection of claims 1, 2, 4 and 16 under 35 U.S.C. §112, second paragraph has been overcome by the above amendments to the claims.

Claims 1 and 7-11 were rejected under 35 U.S.C. §103 (a) as being unpatentable over WO96/02545 to Dondio et al. (hereinafter also referred to as "Dondio"). Dondio fails to render obvious the present invention since among things, Dondio does not explicitly disclose the claimed pyrrolomorphinans and thienomorphinans and the antagonist activity at the opioid delta receptor in the MVD possessed by compounds of this invention.

WO96/02545 specifically discloses only pyrrolomorphinans (pyrrole ring fused to a morphinan unit). Indeed, all of the 19 specifically mentioned compounds are pyrrolomorphinans. Despite this exclusive focus on pyrrolefused morphinans, Dondio alludes to generic literature methods to synthesize various other heterocycles such as pyridine, pyrazine, thiophene, furan and imidazole (Schemes 3-8).

Eventhough the generic disclosure of Dondio might encompass the claimed compounds, because of the vast number of compounds encompassed by Dondio, the claimed compounds are not fairly suggested or rendered obvious. Clearly the preferred compounds of Dondio are quite different from those of the present invention.

Among these lines, the Examiner's attention is kindly directed to *In re Baird* 29USPQ2d 1550 (Fed. Cir. 1994).

In Baird, the compound recited in the claims (i.e.-bisphenol A) was within the same of the genus (i.e.-diphenols) disclosed in the prior art. However, just as in the present case, the specific preferred prior art compounds differed from that of the claims. Therefore, because the genus encompassed a large number of possible compounds, analogous to the present case, the Court found that the claims were non-obvious.

Moreover, the primary biological focus of the compounds described in WO 96/02545 relates to the *pyrrolomorphinans* possessing agonist activity at the opioid delta receptor (page 8, lines 17-20 in WO 96/02545). Although there is a statement "these compounds displayed also potent delta agonist or antagonist properties in the MVD preparation" (page 11, lines 36-38), the only compound (compound 7) for which pharmacological characterization in the MVD is given shows that this compound is a potent agonist at the receptor (page 12, lines 2-3).

In contrast, the present invention describes, for instance, *thienomorphinans* possessing antagonist activity at the opioid delta receptor in the MVD (see compounds **8a-8f** in Table 3). These compounds are very weak as agonists at the mu receptor in the MVD (0%-15% maximum stimulation at 10 uM) and at the mu receptor in the GPI (0%-40% maximum stimulation at 10 uM). Among compounds **8a-8f**, the profile of 8d is that of a mixed antagonist/agonist ligand with high antagonist activity at the delta receptor in the MVD ($K_e = 5.0$ nM) and with no antagonist but modest agonist activity at the delta receptor in the GPI (40% maximum stimulation at 10 uM). Such mixed delta antagonist/mu agonist ligands are of potential interest as analgesic agents that may be devoid of tolerance and dependence side effects. They are also

of interest as modulatory agents for preventing the development of tolerance and dependence for mu agonist analgesics such as morphine. With respect to the pyridomorphinans, please see compounds **7a-7f** in Table 3.

Thus the chemical entities (pyrrolomorphinans vs thienomorphinans and pyridomorphinans and the biological activity profile of the compounds (delta agonists vs delta antagonists) described in WO 96/2545 and the present application are quite different.

This diametrically opposite activity overcomes the assertion of obviousness stated in the Office Action. Along these lines, see *parte Blattner*, 2 USPQ2d 2047 (BPAI, 1987). In *Blattner*, the invention related to certain aezepene compounds having a 7-membered ring as contrasted to the pyrrolidino and piperidino containing 5-and 6 membered "ring homologs" of the prior art. However, analogous to the present case, the claimed compounds possessed utility that was opposite to that of the reference. Accordingly, the Board found that the diametrically opposite utilities overcome an assertion of prima facie obviousness which rises from the expectation that compounds similar in structure will have similar properties. Also see *In re May* 197USPQ601 (CCPA 1978).

In addition, the case law referred to by the Examiner does support the rejection of the claims in view of the difference in the facts in this case as compared to those in the case law cited in the Office Action.

For instance in the cases of, *In re Susi*, *In re Malagari*, *In re Rosicky*, *In re Fracalossi*, and *In re Lamberti*, the applicant did not present evidence that was deemed to be of the type needed to rebut a prima facie case of obviousness. As mentioned above, compounds of this invention exhibit properties that are the opposite of those of the reference.

On the other hand, *In re Lemin* and *In re Rinehart*, also relied upon in the Office Action, if anything, support patentability of the present invention. In both of these cases, claims were deemed to be patentable, even though they were within the genus of the prior art.

Also, the cited art lacks the necessary direction or incentive to those of ordinary skill in the art to render under 35 U.S.C. 103 sustainable. The cited art fails to provide the degree of predictability of success of achieving properties, such as antagonist activity at the opioid delta receptor in the MVD, attainable by the present invention needed to sustain a rejection under 35

U.S.C. 103. See *Diversitech Corp. v. Century Steps, Inc.* 7 USPQ2d 1315 (Fed. Cir. 1988), *In re Mercier*, 185 USPQ 774 (CCPA 1975) and *In re Naylor*, 152 USPQ 106 (CCPA 1966).

Moreover, properties of the subject matter and improvements which are inherent in the claimed subject matter and disclosed in the specification are to be considered when evaluating the question of obviousness under 35 U.S.C. 103. See *Gillette Co. v. S.C. Johnson & Son, Inc.*, 16 USPQ2d. 1923 (Fed. Cir. 1990), *In re Antonie*, 195, USPQ 6 (CCPA 1977), *In re Estes*, 164 USPQ (CCPA 1970), and *In re Papesch*, 137 USPQ 43 (CCPA 1963).

No property can be ignored in determining patentability and comparing the claimed invention to the cited art. Along these lines, see *In re Papesch*, supra, *In re Burt et al*, 148 USPQ 548 (CCPA 1966), *In re Ward*, 141 USPQ 227 (CCPA 1964, and *In re Cescon*, 177 USPQ 264 (CCPA 1973).

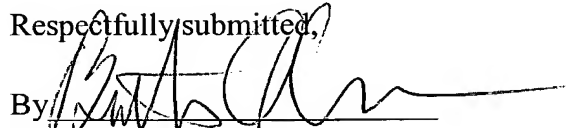
Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 22-0185, under Order No. 21381-00053-US from which the undersigned is authorized to draw.

Dated: 4-15-03

Respectfully submitted,

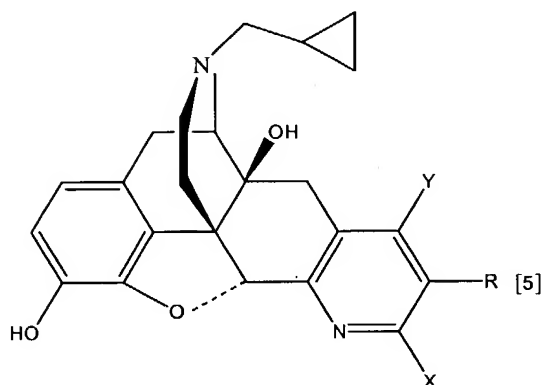
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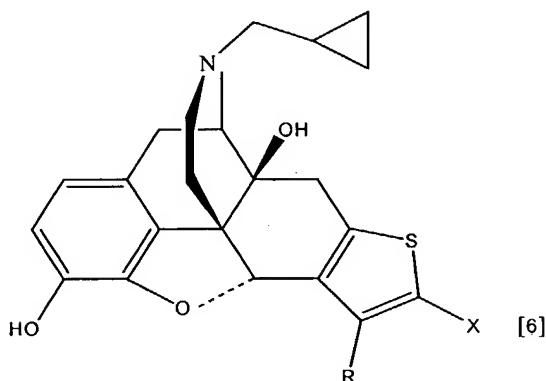
Version With Markings to Show Changes Made**In the Claims**

Please amend claim 1 as follows:

1. (Amended) A compound represented by the formulae:



I; and



II

wherein each of Y, X and R individually is selected from the group consisting of hydrogen, hydroxy, halo, CF₃, NO₂, CN, NH₂, COR¹ and CO₂R² wherein R¹ is selected from the group consisting of alkyl, aryl, alkaryl, and NH₂, and R² is selected from the group consisting of alkyl, aryl, and aralkyl, and provided that at least one of Y, X and R in formula I is other than hydrogen; [and] or pharmaceutically acceptable [salts] salt thereof.

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